sequence selected from SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5 or SEQ ID NO: 7 to SEQ ID NO: 1035, or

SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO: 7 to SEQ ID NO:1035, wherein at least one mononucleotide is linked or modified by one or more of phosphorothioate, phosphorodithioate, phosphorotrithioate, methylphosphonate, phosphoramidate, boranophosphate, phosphotriester, formacetal, 2'-O-methyl, thioformacetal, 5'-thioether, carbonate, 5'-N-carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene (methylimino) (MMI) and methyleneoxy (methylimino) (MOMI), terminal 1,3-propanediol, terminal dodecanol, 2'-O-methoxyethyl, C-5-propynyl pyrimidine, C-5 methyl cytidine, C-5 ethynyl pyrimidine, 2'-propoxy, C-18 amine, N3'-P5' phosphoramidates, 3'-alkylamino, 2'-fluoro; 5-fluoro pyrimidine, 5-iodo pyrimidine, 5-bromo pyrimidine, 2'-borano, C-5 hexynyl pyrimidine, 2'-O-(2-methoxy)ethyl, 2'-O-aminopropyl, 5-(phenylethyl) or peptide nucleic acid interbase linkages or conjugated to a polyethylene glycol, cholesterol, cholesteryl, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEASulfate), dehydroepiandrosterone sulfatide (DHEA Sulfatide), ubiquinone (CoQn), dolichol, poly L-lysine, sulfatidic acid or fatty acids. --.

C22 cont

SUB F23 Cont

ADD D17

REMARKS

THE INTERVIEW

The applicant thanks Drs. Epps and LeGuyader for the interview granted his attorney on January 31, 2001. The attorney had faxed earlier draft claims to the examiners, which were discussed during the course of the interview. The attorney explained that no new search is needed because all the language added to the claims or the newly added claims are supported by the previously existing claims. For example, device claims have been added whereas kit claims comprising a device existed, and the like. The present claims have been amended to incorporate the suggestions provided by Drs. Epps and LeGuyader. The attorney pointed out that the application as filed incorporates by reference all priority documents, as indicated at page 10, lines 12-14 of the application as filed. This statement, specifically placed in the text of the original application because its text incorporates information from four separate cases, supports

the applicant's prior amendment to incorporate text from one of the priority cases by reference into the present specification and the Sequence Listing section. In addition, all other rejections of the claims were discussed, including the patentably distinguishing characteristics of the present method of delivering a formulation of critical particle size versus the Bennett patent simply providing boiler plate description of routes of administration. Agreement was reached on the scope and enablement issues as well as on the patentability of the claimed invention over the cited reference. The attorney then proceeded to the several double patenting rejections. She pointed out that the applicant had already submitted a Terminal Disclaimer (TD) over the prior commonly assigned patents and indicated that no further action seemed to be required. Upon inspection of the case's file history, the examiners concurred and indicated that the TD had been accepted and that the rejections over the prior patents were unmerited. In addition, the examiners agreed to consider the newly added claims in view that they did provide no new material requiring further searching. The following remarks contain the substance of the arguments exchanged during the interview and an expansion thereof.

THE PENDING CLAIMS

Claims 108-219 were pending, various claims have been amended, claims 132, 142, 145, 147, 149-150, 157, 160, 174, 177, 182, 191, 194 and 199 have been deleted, and claims 220-225 were added. Accordingly, Claims 108-131, 133-134, 146, 148, 151-156, 158-159, 161-173, 175-176, 178-181, 183-193, 195-198 and 200-225 remain pending in this case. The applicant requests reconsideration of the rejections in light of the above amendments and the following remarks and allowance of the pending claims.

THE OBJECTIONS TO SPECIFICATION AND CLAIMS

1- Objections to the Added Disclosure

The examiner objected to the amendments made to the specification on May 4, 2000. The specification of this patent application, as filed, contains a statement incorporating by reference the texts of all documents of which priority is claimed as indicated by the Oath/Declaration in this case. The text referred to is as follows:

> **The relevant sections of the disclosures of the above cited, and of all other patents and references cited in this patent are incorporated herein by reference.** See, page 10, lines 12-14 of the original application.

The amendments made by the applicant in the previous response are, therefore, in compliance with the rules. The applicant is enclosing a clean copy of the substitute application along with the requisite declaration. The applicant is also enclosing a copy of a previously filed claim for priority and a substitute Declaration including references to the prior applications, and requests a corrected filing receipt.

The examiner also objected to the addition of several surfactants listed at pages 2-3 of the Office Action. The applicant has deleted those entries, whose addition was made in error.

2- Objections to the Claims

Claims 172, 185 and 199 stand objected to. These claims have been amended and are believed to be free of this rejection grounds.

3- Objections to the Sequence Listing

As discussed during the interview, the specification was appropriately amended to introduce targets and exemplary oligonucleotides that were disclosed in one of the parent applications, USSN 08/474,497 filed June 7, 1995, now U.S. Patent No. 5,994,315, whose text was incorporated by reference. The Sequence Listing submitted previously by the applicant contained the sequences present in the application as filed, as well as those sequences incorporated by reference. Accordingly, the added sequences were properly added as supported by the priority application. Moreover, the Declaration submitted previously related the correct status of the text of the sequences.

THE INDEFINITENESS REJECTION

Various claims have been rejected under 35 U.S.C. 1.112, second paragraph, allegedly because their language is indefinite. This rejection is partially traversed.

The rejected claims have been either amended or deleted to more clearly describe the claimed subject matter.

The examiner's attention is called to claim 108 (directed to a composition including oligos anti-sense to adenosine receptor targets), which claim is of more limited scope than claims 164, 173 and 222 (broadly encompassing a device, kit and administration of antisense oligos associated with certain properties). In the examiner's comments this fact seems to have been overlooked, and all claims were discussed similarly.

This rejection is believed to have been overcome by these amendments.

THE ENABLEMENT REJECTION

Claims 108-219 stand rejected under 35 U.S.C. 1.112, first paragraph, due to their breadth. This ground is traversed with regards to the pending claims.

The claims have been amended as indicated during the interview, and are believed to be free from the above ground of rejection. The product claims are limited to oligos anti-sense to adenosine receptors administered in the form of an aerosol. The language of the composition claims is fully supported by the application as filed and by has been thoroughly exemplified in the three Nyce Declarations with respect to several different oligos directed to one target, and to different targets within the scope of the claims. The disclosure also contains other targets, which the exminer would not allow to be incorporated into the claims, as require further searching. These claims also contain limitations relating to activities or symptoms associated with the adenosine receptor targets and, therefore, should not be subject to the above rejection. The specification is fully enabling of the composition as claimed, as it teaches how to make and use the inventive product.

The device, kit and method claims (claim 164 et seq.), are broader in scope. They are fully supported by the 44 different targets, whose exemplary sequences are part of the specification upon their prior incorporation by reference from one of the priority documents. Claims 164 et seq. require the delivery of a specific formulation of particle size about 0.5 to about 500 microns of an anti-sense oligo targeted to DNA or mRNA encoding a protein associated with hyper-responsiveness to and/or increased levels of adenosine, bronchoconstriction, lung allergies or inflammation or asthma for administration to the airways to diagnose and treat these symptoms. The applicant has

shown that this specific type of formulation having particles of the required size provides unexpected results for its intended use. See the 3 Nyce Declarations and the Nyce and Metzger, Nature article made of record herewith. As pointed out above, the showings include, contrary to the exminer's statement, several oligos anti-sense to one target and oligos directed to several different targets, including adenosine A1, A2b and A3 receptor targets, and to the bradykinin B2 receptor. These showings do not seem to have been fully considered based on the examiner's statement that "only one functional antisense ..." is described and exemplified. The consistent results obtained for different targets clearly demonstrate the broad applicability of the claimed method.

The examiner relies on the Crooke reference for her arguments. The article cited by the examiner is a general background deascription of the field of anti-sense technology, where the author describes, as lecturing to a class, the abc of anti-sense. Crooke clearly starts by indicating that his comments relate to a hypothetical effect as evidenced by his stating that those **"factors that <u>may</u> influence experimental <u>interpretations</u>" of their mechanism of action** (emphasis added). See, page 1, Section B. That is, the interpretation of results as they provide hints of a mechanism of action, not the results themselves. Crooke himself, notwithstanding, provides a list of techniques and procedures that he recommends for demonstration of disappearance of the target RNA. See, page 4, Section II. Recommendations. Finally, Dr. Crooke's comments relate to in vitro experiments geared to the difficulties encountered in elucidating the mechanism of action of anti-sense molecules.

The applicant is enclosing an article by Dr. Nyce, namely "Chapter 25, Emerging Drugs: The Prospect for Improved Medicines", pp. 465-375, Ashley Publications Ltd. ISSN 1361-9195 (1998). In this article Dr. Nyce reviews the historical development of antisense technology, from its beginnings to the present time. In it, he describes the numerous antisense drugs that are being subject to clinical trials, including several by Dr. Crooke's company "Isis". See, for example, page 366, last paragraph (chemical modifications to anti-sense molecules from Hybridon and ISIS, Dr. Crook's company), page 367, 3rd. paragraph from last (ISIS 5320 from Dr. Crooke's company and GEM 92 from Hybridon for HIV infection), page 368, 3rd. paragraph. (ISIS 3521, ISIS 5132 and ISIS 5320 from Dr. Crooke's company, GEM 231 from Hybridon and LR-3001 and LR-

4437 from Lynx for cancer), page 368, last paragraph (ISIS 2302 from Dr. Crooke's company for inflammation). Clearly, Dr. Crooke has not been deterred by his general comments on topics of basic science for the development of several antisense drugs that have, as of 1998, demonstrated clinical efficacy and lack of toxicity.

But Dr. Nyce's article is better employed as a reference for what the difficulties are in employing anti-sense drugs in therapy. He mentions stability, toxicity and delivery of the drugs, with delivery by far being singled out as the greatest obstacle to success. In Dr. Nye's own words:

> The greatest obstacle to effective development of antisense oligonucleotides as therapeutics relates to the difficulty in delivering quantities of the drug to the target tissue sufficient to achieve attenuation of the target mRNA. Page 371, 3rd. paragraph.

And he goes on to advance that dir3ct delivery to a targeted area will resolve the problems brought about by extensive systemic transit of a drug. He states that potential solutions are, for example, topical administration for skin disorders. Again, ISIS, Dr. Crooke's company is developing a drug for treating soriasis, ISIS 2302. Further,

> ...direct delivery to the target organ, e.g. via inhalation of respirable antisense oligonucleotides in the treatment of lung disorders. Page371, 3rd. paragraph.

Dr. Nyce then goes on to explain the advantages of the RASONs (respiratory antisense oligonucleotides) described in this and other patent applications. Dr. Nyce's EPI 2010 is now undergoing clinical trials, after extremely successful pre-clinical trials.

In summary, if the difficulties in delivering antisense oligos to their intended targets were significant, Dr. Nyce's invention has taken the field of delivering antisense oligos with therapeutic results beyond the prior art represented by Dr. Crooke's 1998 article, by teaching that direct administration to the area of interest is critical for attaining a high degree of success.

Dr. Nyce has been successful in delivering each anti-sense oligo tested to its intended target, as well as in attaining the sought effect. He demonstrated this with several different oligos, which work is shown in the 3 Nyce Declarations, as well as with oligos targeted to other mRNAs. Moreover, Crooke himself by the fact that

he is carrying many anti-sense oligos through clinical trials, at great cost to his company, counters the examiner's selected comments lifted from his article. Whether it is the applicant or others that have or will test some of the oligos anti-sense to specific targets is irrelevant. What the applicant has shown is that by administering into the airways any oligo anti-sense to a lung target he can reach that target, deliver the oligo and elicit a therapeutic response. Whether the oligo is associated with one or the other target is irrelevant, as long as the lung is involved the respiratory delivery will take the oligo to its target.

While Crooke was busy reporting on his general thoughts and comments as to the difficulties encountered on the road to success, the applicant discovered the key to delivering an oligo to its intended target, such as through the respiration to reach the lung, topically to reach the skin, and the like. Further, although demonstrated for every oligo tested (different oligos inhibit the same target, and each oligos designed for this purpose inhibits the target for which it was designed), the US Patent Law does not require that each and every oligo included in the claimed genus actually bind to the target nucleic acid and provide significant inhibition. Under the Law it is sufficient to make a showing involving some members of a group or genus, but it is not required to show that all members are active; nor is it necessary to show that they all act efficaciously for their intended purpose (or target). It suffices to enable them in their preparation and exemplary use.

The above rejection is thus believed to be moot.

THE ANTICIPATION REJECTION

Claims 108-111 and 173-175 stand rejected under 35 USC 1.102(e), allegedly because they are anticipated by Bennett (US Pat No. 5,514,788). This ground of rejection is traversed in so far as it relates to the pending claims.

The Bennett patent is different from the claimed invention, and fails to render it obvious. Bennett relates to three targets and their anti-sense oligos: ICAM-1, VCAM-1, and ELAM-1. Bennett, in fact, provides boiler-plate wording relating to "intranasal" delivery and delivery "by inhalation" and indicates that "It has been hoped that inhibitors

of ICAM-1, VCAM-1 and ELAM-1 expression would provide a novel therapeutic class of anti-inflammatory agents" for example against asthma, although no in vivo data was provided. Nowhere does the Bennett patent describe or suggest the need or advantage of delivering through the airways the applicant's specific formulation of particle size about 0.5 micron to about 500 micron (0.5-10 microns for the smaller particles inhaled into the lungs and 10-500 microns for the nasally administered particles) to critically improve the amount of oligo that reaches the target, and the efficacy attained. Nor does Bennett mention or suggest the incorporation of a surfactant into its composition. Bennett makes no mention of the surfactant claimed by the applicant. The claimed composition requeires a surfactant, which use is not obvious over Bennett.

The above rejection is believed to be moot in view of the above remarks in so far as it applies to the pending claims.

THE AMENDMENTS TO THE CLAIMS

The amendments to the claims and the newly added claims are fully supported by the specification as filed and the existing claims. No new subject matter is believed to have been added.

GENERAL REMARKS

No additional fee is believed to be owed for extra claims. The Assistant Commissioner is, however, hereby authorized to charge any fees owed, or refund any excess, to Deposit Account No. 50-1728, including a fee for an extension of time that, if needed, is hereby requested.

In view of the foregoing amendments and remarks, this application is believed to be in condition for examination and allowance. Early notice to this respect is solicited.

Respectfully submitted,
EPIGENESIS PHARMACEUTICALS, INC.

February 1, 2001
Date

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I hereby certify that this correspondence is being deposited with the United States Postal Service, Express Mail Post Office to Addressee, Express Mail Label EL836372442US, in an envelope addressed to the Assistant Commissioner for Patents, 1911 S. Clark St., Crystal Mall 1, Receptionist 7th Floor, Arlington, VA 22202, on February 6, 2001, by Dee Dee Sutherland.

SIGNATURE

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